PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100885- 1 wo	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE 03/01705	International filing date *(day/month/year)* 05.11.2003	Priority date *(day/month/year)* 07.11.2002
International Patent Classification (IPC) or both national classification and IPC C07D211/70		
Applicant ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 14.05.2004	Date of completion of this report 29.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Gavriliu, D Telephone No. +49 89 2399-8274

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE 03/01705

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-77 as originally filed

Claims, Numbers

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 15-17(with respect to industrial applicablity)

   because:

   ☒ the said international application, or the said claims Nos. 15-17 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-14,18-23
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For reasoning with regards to unsearched subject-matter, see Form PCT/ISA/210 of the International Search Report. No International Preliminary Examination will be carried out with respect to subject-matter which is not covered by the search report (Rule 66.1(e)PCT).

Claims 15-17 relate to subject-matter considered by this Authority to be covered by the provision of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claims(article 34(4)(a)(i)PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Reference is made to the following documents:**

   D1: WO 98 28275 A1

2. **Novelty** (Article 33(1) and (2)PCT)

   The present subject-matter relates to compounds of formula(I) as as opioid receptors ligands (see present Claim 1).

   The present compounds can be considered as novel over the D1 compounds on the account of the anilin-3-yl moiety, which is in the present case at least mono substituted on the nitrogen atom.

3. **Inventive step** (Article 33(1) and (3)PCT)

   The present application discloses piperidin-4-ylidene derivative of formula (I) (see present Claim 1) as opioid ligands (δ-receptor), useful to treat pain, anxiety or functional gastrointestinal disorders.

   D1, which is regarded as the closest prior art, discloses compounds of formula (I)(see Claim 3), wherein A is a phenyl ring substituted with a N-diethylamide

moiety (as in the present case) and B can be a phenyl moiety substituted with a -(CH2)qNR4R5 moiety(wherein q=0)(as for the present compounds). Moreover D1 discloses N, N-diethyl-4-(3-aminophenyl-piperidin-4-ylidene-methyl)-benzamide(see page 115 of D1), compound which differs from the present compounds only through the unsubstitution of the amino function of the aniline moiety. The compounds disclosed by D1 are also known as delta opioid receptor ligands, useful to treat the same diseases as in the present case.

The technical problem underlying the present application cannot be seen as a provision of piperidin-4-ylidene derivatives, useful as delta opioid ligands for the following reasons:

The present application discloses compounds which differ from the D1 compounds only through the substitution on the above-mentioned nitrogen atom with substituents (R1, R2) which can present very different chemical structures (therefore they seem not to be important for the maintaining of the claimed activity). Consequently, the skilled person would have expected that the same qualitative effect be maintained in such similar compounds.

An inventive step cannot be recognized as it is not yet shown by appropriate information, e.g. in form of experimental data, that substantially all the claimed compounds have un unexpected property or improved activity over the structurally closest prior art compounds (D1-corresponding N-unsubstituted analog), which is attributable to the distinguishing feature of the invention.

4. **Industrial applicability** (Article 33(4)PCT).

For the assessment of the present claims 15-17 on the question whether they are industrial applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may also allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.